TOXICOLOGY
Urine Drug Testing

LEGAL AID INFORMATION SESSION
Neville Bailey
Forensic & Scientific Services
Coopers Plains
TOXICOLOGY

• Detection of drugs in biological fluids
  Qualifications science degree majoring in chemistry
  this provides a fundamental expertise in analytical techniques and instrumental chemistry

• a knowledge of Pharmaco-kinetics
  [ie how the drugs distribute throughout the body and eliminate from the body (drug metabolism the action of the body on drugs)]
  Knowledge largely derived from additional university study and extensive reading of specific scientific literature

Pharmacology is the study of the action of drugs on the body (Forensic Medical Officers best qualified to comment on effects of drugs eg impairment)
SCHEMATIC OF SYSTEMIC BLOOD CIRCULATION

INHALATION

INJECTION

LUNGS / NASAL

HEART

OTHER TISSUES

KIDNEY

RENAL EXCRETION

GASTRO-INTESTINAL MEMBRANE

LIVER

BILE

METABOLITES

ORAL

ARTERIAL BLOOD

VENOUS BLOOD
SPECIMEN TYPES FOR DRUG ANALYSIS

- **BLOOD:** Primary specimen of choice
- **URINE:** Most common specimen collected in workplace environment
- **BREATH:** Primarily used for alcohol testing
- **ORAL FLUID:** Emerging technology within the workplace environment as alternative to urine
- **HAIR:** Provide a history of drug use / Time line
- **SWEAT:**
MANIPULATION OF THE URINE SPECIMEN

• Individuals who use drugs can be interested in concealing their drug use through manipulation of the urine test.

• Involve substitution / water dilution of urine specimen

• Certain adulterants can affect testing of specific drugs in immunoassay testing (both onsite or laboratory based)

• The use of a substance (adulterant) that will eliminate traces of drug from the urine or otherwise modify the urine so that certain substances are not detected.

• Generally manipulation of a urine specimen can be detected
## INTEGRITY OF URINE SPECIMEN

**INTECT 7**

*(STRIP PANEL FOR ADULTERANT DETECTION)*

<table>
<thead>
<tr>
<th></th>
<th>Bleach</th>
<th>Ammonia</th>
<th>Water</th>
<th>Vinegar</th>
<th>Klear</th>
<th>Urine Luck</th>
<th>Stealth</th>
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<tbody>
<tr>
<td>Creatinine</td>
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<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Nitrite</td>
<td>N</td>
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<td>A</td>
<td>N</td>
<td>N</td>
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<td>Glutaraldehyde</td>
<td>N</td>
<td>N</td>
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<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
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<td>Ph</td>
<td>N</td>
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<td>A</td>
<td>N</td>
<td>N</td>
<td>N</td>
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<td>S.G.</td>
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<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Bleach</td>
<td>A</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>PCC</td>
<td>A</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
</tbody>
</table>

A = Abnormal response

Pearce; J.Anal. Tox, Vol 26, 2002

**TEMPERATURE  [33 TO 38 DEG CELCIUS]**

**CREATININE AND SPECIFIC GRAVITY**
The effects of water dilution on drug testing results were clearly evident in the current study. Subjects consistently produced dilute specimens upon drinking large volumes and drug metabolite concentrations declined below cutoff concentrations.

Cone; J. Anal Tox, Vol 22, 1998
6.9% of urine creatinine levels less than 200 mg/l [or 20 mg/dl]

Source: Laboratory Data
CURRENT STANDARD | 50 - 200 MG/L | MAY INDICATE DILUTION IN SOME INDIVIDUALS. DOES NOT NECESSARILY REPRESENT A DELIBERATE ATTEMPT AT DILUTION

| LESS THAN 50 MG/L | FURTHER TESTING FOR DILUTION REQUIRED REGARDED AS NOT CONSISTENT WITH HUMAN

*A URINARY CREATININE CONCENTRATION SHALL BE MEASURED

AUSTRALIAN STANDARD AS/NZS 4308:2008
DRUG TEST PROCEDURES: IMMUNOASSAY

• Immunoassay has wide application within urine drug testing and more recent applications within oral fluid testing.

• Initially laboratory based however now commonly in wide-spread use for on-site testing.

• Rapid and convenient method to screen large numbers of specimens in a variety of matrices.

• The differentiation of negative specimens

• Limited generally to detection of drug classes
Immunoassays are based on the interaction of a target molecule (antigen) with the corresponding antibody.

Drug analysis uses antibody specific for the drug class analysed together with a labelled form of the same drug.

Competitive reaction is established whereby the drug in the specimen competes with the added labelled drug for the antibody.

The labelled form of the drug is responsible for generating a measurable signal. Where the drug is labelled with an enzyme or a fluorescent substance, the measurement is observed by spectrophotometry.

The proportion of labelled drug bound is inversely proportional to the amount of drug present in the specimen.
DRUG CLASS WITH SIMILAR STRUCTURE CROSS-REACTIVITY (BENZODIAZEPINES)
DRUG CLASS WITH SIMILAR STRUCTURE
SENSITIVITY (BENZODIAZEPINES)

DRUGS WITHIN A CLASS WILL HAVE A DIFFERENT RESPONSE
EFFECT OF CUTOFF VALUE ON DETECTION WINDOW

WHEN IS A DRUG DETECTED?

- 100 NG / ML
- 50 NG / ML
- 25 NG / ML
SIMILARITY OF CHEMICAL STRUCTURE

MORPHINE AND CODEINE CROSS REACT WITH REAGENTS IN AN OPIATE IMMUNOASSAY KIT TO PRODUCE A POSITIVE RESULT
3 MONOACETYL MORPHINE

SYNTHESIS OF HEROIN FROM OPIUM POPPY EXTRACT (ACETYLATION)

HEROIN

ACETYL CODEINE

CODEINE

MORPHINE
THEBAINE
ACETYL CODEINE
METABOLISM OF HEROIN
HEROIN
ACETYL CODEINE
6 MONOACETYL MORPHINE
CODEINE
MORPHINE
PHARMACOKINETIC PROFILE OF HEROIN METABOLISM IN BLOOD FOLLOWING A HEROIN INTRAVENOUS ADMINISTRATION
METABOLISM OF MORPHINE

IDENTIFY MORPHINE USE WHEN MORPHINE & GLUCURONIDE METABOLITES DETECTED IN URINE
METABOLISM OF CODEINE

CODEINE

MORPHINE
CONCENTRATION OF CODEINE V’S RATIO OF THE CONCENTRATION OF MORPHINE TO CODEINE IN URINE SPECIMENS FOLLOWING CODEINE ADMINISTRATION

HOWEVER FROM THE DATA IT IS ALSO OBSERVED THAT MORPHINE CAN BE DETECTED AT CONCENTRATIONS > CODEINE

IN MOST CASES CODEINE IS THE MAJOR DRUG DETECTED
ELIMINATION OF MORPHINE AND CODEINE IN URINE FOLLOWING A CODEINE ADMINISTRATION

MORPHINE HAS A LONGER HALF-LIFE THAN CODEINE
POTENTIAL SOURCE OF AN OPIATE FOLLOWING
THE DETECTION OF A CONCENTRATION OF
MORPHINE THAT IS LESS THAN 1500 NG/ML YET
GREATER THAN CODEINE IN URINE

- Residual levels detected following codeine administration
  (24 to 48 hours)
- Levels consistent with consumption of poppy seed on bakery
  products (buns, rolls, bread)
- Residual levels detected following heroin administration
  - Use of morphine in conjunction with any of the above

NOTE: Codeine present in combination with other drugs in
medications that require prescription

Morphine requires a prescription
INTERPRETATION OF MORPHINE / CODEINE CONCENTRATION

MORPHINE > CODEINE [RATIO > 1]
MORPHINE CONCENTRATION LESS THAN 2000 NG/ML
UNABLE TO IDENTIFY THE SOURCE OF THE OPIATE

2,000 NG / ML
THE DETECTION OF MORPHINE AND CODEINE IN THE URINE AT LEVELS LESS THAN 2000 NG / ML COULD REFLECT THE USE OF MORPHINE, HEROIN, CODEINE OR INGESTION OF POPPY SEEDS; THE IDENTITY OF THE ORIGINAL DRUG CONSUMMED CANNOT BE DETERMINED
# DATA FOR INTERPRETATIVE CONSIDERATION

<table>
<thead>
<tr>
<th></th>
<th>MORPHINE (NG/ML)</th>
<th>CODEINE (NG/ML)</th>
<th>CREATININE (MG/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAY 1</td>
<td>&lt;110,000</td>
<td>3200</td>
<td>1430</td>
</tr>
<tr>
<td>DAY 7</td>
<td>30,000</td>
<td>20,000</td>
<td>1410</td>
</tr>
<tr>
<td>DAY 15</td>
<td>28,000</td>
<td>22,000</td>
<td>1370</td>
</tr>
</tbody>
</table>
METABOLISM OF DIAZEPAM (VALIUM)

**DIAZEPAM**

**TEMAZEPAM**

**NORDIAZEPAM**

**OXAZEPAM**
URINE TOXICOLOGY CONFIRMATION REPORT

Client: Burleigh Heads Community Corrections
Name: DOB: 23-Nov-
LIMS No.
Date Collected: 08-Feb-05
Date Received: 11-Feb-05 Sample Sealed: Yes

Creatinine

Benzodiazepine Confirmation (LCMS)

NORDIAZEPAM 400 ng/ml
TEMAZEPAM 300 ng/ml
OXAZEPAM 300 ng/ml

Lenore Hadley
Analyst
Queensland Health Scientific Services
Brisbane
16-Feb-05

THE BENZODIAZEPINE RESULT IS CONSISTENT WITH THE USE OF VALIUM
Intended Use

The DRI® Opiate Assay is intended for the qualitative and semiquantitative determination of opiates in human urine.

The assay provides only a preliminary analytical test result. A more specific alternative chemical method must be used in order to obtain a confirmed analytical result.

Gas chromatography/mass spectrometry (GC/MS) is the preferred confirmatory method.1,2

Clinical consideration and professional judgment should be applied to any drug of abuse test result, particularly when preliminary positive results are used.
BENZODIAZEPINE CLASS OF DRUGS

DIAZEPAM
NORDIAZEPAM
OXAZEPAM
TEMAZEPAM
CLONAZEPAM
NITRAZEPAM
FLUNITRAZEPAM

ALPRAZOLAM
TRIAZOLAM
MIDAZOLAM
BROMAZEPAM
LORAZEPAM
CLOBAZAM
FLURAZEPAM
<table>
<thead>
<tr>
<th>AMPHETAMINE TYPE SUBSTANCES</th>
<th>MDMA (METHYLENE DIOXYMETHYL AMPHETAMINE)</th>
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</thead>
<tbody>
<tr>
<td>AMPHETAMINE</td>
<td>MDA</td>
</tr>
<tr>
<td>METHYLAMPHETAMINE</td>
<td>MDEA</td>
</tr>
<tr>
<td>PHENTERMINE</td>
<td>BDMA</td>
</tr>
<tr>
<td>FENFLURAMINE</td>
<td>PMA</td>
</tr>
<tr>
<td>EPHEDRINE</td>
<td>DMA</td>
</tr>
<tr>
<td>PSEUDOEPHEDRINE</td>
<td>BDMPEA</td>
</tr>
</tbody>
</table>
**PRINCIPLES OF GAS CHROMATOGRAPHY MASS SPECTROMETRY (GCMS)**

- As compounds (drugs) elute from the column into the collision chamber of the mass spectrometer they are bombarded with a high energy electron beam.
- The electron beam imparts energy to the compounds which then fragment into smaller ion charged particles that are separated within an oscillating magnetic field based on their mass to charge ratio.
- The particles are collected by the detector as they pass through the field and provide a characteristic pattern for a particular compound (drug fingerprint).
Identification of a compound is achieved when the fragmentation pattern is compared against a library of known drug fragmentation patterns.

**Mass Spectrometry**

- **Morphine**
  - $\text{M}^+ = 285$
  - Key fragments: 124, 162, 288

- **Codeine**
  - $\text{M}^+ = 299$
  - Key fragments: 124, 162, 289

**Chromatography**
LIQUID CHROMATOGRAPH

ELECTROSPRAY INTERFACE

IN-LINE MASS SPECTROMETER
ANALYSIS TIME IN DAYS (WEEKENDS INCLUDED) FOR ALL CORRECTIVE SERVICE SPECIMENS FROM RECEIPT OF SPECIMEN TO REPORT (NOTE: PRIORITY GIVEN TOWARDS DRUG COURT SPECIMENS)
VARIATION OF DRUG CONCENTRATION (CANNABIS METABOLITE) AND CREATININE IN URINE
THCCOOH NORMALISED AGAINST CREATININE
NEW USE DIFFERENTIATED FROM RESIDUAL USE IN OCCASSIONAL CANNABIS SMOKERS

RATIO OF NORMALISED THCCOOH / CREATININE DAY X+
NORMALISED THCCOOH / CREATININE DAY X

RATIO 1.5

RATIO 1.83 (< 20 CREATININE)
RATIO 2.09
RATIO 0.76

REDUCED CHANCE OF DETECTION OF OCCASSIONAL CANNABIS USAGE IF INTERVAL BETWEEN COLLECTION EXCEED 3 DAYS
<table>
<thead>
<tr>
<th>DAYS BETWEEN TESTS</th>
<th>THC-COOH (NG/ML)</th>
<th>THC-COOH NORMALISED AGAINST CREATININE</th>
<th>RATIO NORMALISED CURRENT TO PREVIOUS</th>
<th>CREATININE (MG/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>23.9</td>
<td>23.9</td>
<td>23.9</td>
<td>920</td>
</tr>
<tr>
<td>43</td>
<td>16</td>
<td>15.5</td>
<td>0.6</td>
<td>1030</td>
</tr>
<tr>
<td>35</td>
<td>130</td>
<td>481.5</td>
<td>31</td>
<td>270</td>
</tr>
<tr>
<td>34</td>
<td>450</td>
<td>750</td>
<td>1.6</td>
<td>600</td>
</tr>
<tr>
<td>14</td>
<td>190</td>
<td>575.8</td>
<td>0.8</td>
<td>330</td>
</tr>
<tr>
<td>15</td>
<td>1525</td>
<td>837.9</td>
<td>1.5</td>
<td>1820</td>
</tr>
<tr>
<td>6</td>
<td>970</td>
<td>461.9</td>
<td>0.6</td>
<td>2100</td>
</tr>
<tr>
<td>8</td>
<td>115</td>
<td>396.6</td>
<td>0.9</td>
<td>290</td>
</tr>
<tr>
<td>13</td>
<td>160</td>
<td>592.6</td>
<td>1.5</td>
<td>270</td>
</tr>
<tr>
<td>23</td>
<td>1800</td>
<td>775.9</td>
<td>1.3</td>
<td>2320</td>
</tr>
</tbody>
</table>
If the carboxy THC concentration in the urine sample collected on the 22/4/08 is normalised to a creatinine concentration of 1640 the corresponding carboxy THC concentration would be of the order of 175.

By way of either creatinine normalisation or viewing the reported result, the concentration of carboxy THC has increased in the urine specimen from that collected on the 22/4/08 to the one collected on the 28/4/08 some 6 days later.

My opinion is that this increase in concentration is not consistent with normal elimination patterns in urine following cannabis use and is consistent with use of the drug within the interval between the two tests.
PASSIVE SMOKING

The concept of a non-smoker passively inhaling nicotine from normal cigarette smoke also applies to side-stream smoke from cannabis cigarettes.

The level of cannabinoids detected through passive exposure experiments is dependent on the concentration of smoke in the air, this is a function of room size and number of cigarettes smoked.
It is possible for urine levels to exceed 20 ng/ml as a result of passive inhalation. The question is to whether these experimental conditions are achieved in real life.

Experimental conditions designed to maximise the exposure and increase the likelihood of passive inhalation.

Closed medium sized station wagon with four subjects each smoking two cigarettes. Two non-smokers exposed to smoke for one hour. 1 urine specimen out of 23 collected over a twenty-four hour period was positive at just above the immunoassay cutoff.
Note from author:

‘IT SEEMS IMPROBABLE THAT SUBJECTS WOULD UNKNOWINGLY TOLERATE THE NOXIOUS SMOKE CONDITIONS PRODUCED BY THIS EXPOSURE’

SMALL UNVENTILATED ROOM (2.1 X 2.5 X 2.4) RESEMBLED THAT OF A BATHROOM

<table>
<thead>
<tr>
<th>Subject</th>
<th>Number of cigarettes</th>
<th>Number of cigarettes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Four</td>
<td>Sixteen</td>
</tr>
<tr>
<td>A</td>
<td>nil</td>
<td>19</td>
</tr>
<tr>
<td>B</td>
<td>nil</td>
<td>15</td>
</tr>
<tr>
<td>C</td>
<td>8</td>
<td>35</td>
</tr>
<tr>
<td>D</td>
<td>nil</td>
<td>20</td>
</tr>
<tr>
<td>E</td>
<td>12</td>
<td>25</td>
</tr>
<tr>
<td>F</td>
<td>n/a</td>
<td>87</td>
</tr>
<tr>
<td>G</td>
<td>n/a</td>
<td>10</td>
</tr>
</tbody>
</table>

Maximum Urine Concentration of THCCOOH (ng/ml) after Passive Exposure for one hour each session to a number of cigarettes over six days.
delta-9-tetrahydrocannabinol (THC) is regarded as the psychoactive principle in cannabis

11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid (THC-COOH) is the inactive metabolite
**TETRAHYDROCANNABINOL (THC) LEVELS IN BLOOD**

Oral fluid cavity is contaminated with THC in cigarette smoke.

<table>
<thead>
<tr>
<th>COLLECTION TIME (HOURS)</th>
<th>THC ORAL FLUID GC-MS (NG/ML)</th>
<th>THC PLASMA GC-MS (NG/ML)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2</td>
<td>5800</td>
<td>193</td>
</tr>
<tr>
<td>0.33</td>
<td>81</td>
<td>145</td>
</tr>
<tr>
<td>0.5</td>
<td>49</td>
<td>51</td>
</tr>
<tr>
<td>1</td>
<td>29</td>
<td>17</td>
</tr>
<tr>
<td>2</td>
<td>3.5</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>3.6</td>
<td>2</td>
</tr>
</tbody>
</table>

*Figure 2. Mean plasma levels of THC, 11-OH-THC, and THCCOOH during and after smoking a single 3.55% THC marijuana cigarette.*
THC LEVELS IN ORAL FLUID AFTER SMOKING CANNABIS

Average data from four passive smokers

Neidbaler; J. Anal Tox, Vol 28, 2004
EQUILIBRIA IS ALSO ESTABLISHED BETWEEN THE DRUG CONCENTRATION IN BLOOD AND ORAL FLUID

ORAL FLUID DRUG DETECTION WINDOW SIMILAR TO DETECTION WINDOW IN BLOOD AS CONCENTRATION DEPENDENT ON BLOOD DRUG CONCENTRATION (EXCEPTION TETRAHYDROCANNABINOL)

<table>
<thead>
<tr>
<th>DRUG</th>
<th>ORAL FLUID TO PLASMA RATIO</th>
</tr>
</thead>
<tbody>
<tr>
<td>THC</td>
<td>0.1</td>
</tr>
<tr>
<td>COCAINE</td>
<td>2</td>
</tr>
<tr>
<td>MORPHINE</td>
<td>0.2</td>
</tr>
<tr>
<td>CODEINE</td>
<td>1</td>
</tr>
<tr>
<td>DIAZEPAM</td>
<td>0.03</td>
</tr>
<tr>
<td>AMPHETAMINE</td>
<td>2.8</td>
</tr>
</tbody>
</table>

THC IS DEPOSITED IN ORAL CAVITY DURING CANNABIS SMOKING
RADIOLABELLED THC THROUGH INTRAVENOUS INJECTION SHOWS LITTLE OF THE ISOTOPE IS DETECTED IN THE ORAL FLUID
POOR RESPONSE TO BENZODIAZEPINES

LIMITATIONS TO SUITABILITY OF ORAL FLUID FOR DETECTION OF ALL DRUGS BY ON-SITE TEST DEVICES
AS/NZ 4308 CUTOFF LEVELS FOR IMMUNOASSAY SCREEN TESTS

A RESULT WITH AN OPIATE VALUE (500) OBTAINED ABOVE THE CUTOFF VALUE (300) WILL BE REPORTED AS DETECTED (POSITIVE) AND A CONFIRMATORY TEST IS REQUIRED.

SIMILARLY AN OPIATE VALUE (250) OBTAINED BELOW THE CUTOFF VALUE (300) WILL BE REPORTED AS NOT DETECTED (NEGATIVE).

<table>
<thead>
<tr>
<th>CLASS OF DRUG</th>
<th>CUT-OFF LEVEL (UG /L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPIATES</td>
<td>300</td>
</tr>
<tr>
<td>AMPHETAMINE TYPE SUBSTANCE</td>
<td>300</td>
</tr>
<tr>
<td>CANNABIS METABOLITES</td>
<td>50</td>
</tr>
<tr>
<td>COCAINE METABOLITES</td>
<td>300</td>
</tr>
<tr>
<td>BENZODIAZEPINES</td>
<td>200</td>
</tr>
</tbody>
</table>
## CUT-OFF LEVELS AS/NZ4308:2008

### CONFIRMATION ANALYSIS REPORTING OF RESULTS

Individual drugs or metabolites confirmed by the laboratory at a concentration greater than the cutoff value nominated in the standard shall be reported as detected.

<table>
<thead>
<tr>
<th>COMPOUND</th>
<th>CUT-OFF LEVEL (UG/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MORPHINE</td>
<td>300</td>
</tr>
<tr>
<td>CODEINE</td>
<td>300</td>
</tr>
<tr>
<td>6-ACETYLMORPHINE</td>
<td>10</td>
</tr>
<tr>
<td>AMPHETAMINE</td>
<td>150</td>
</tr>
<tr>
<td>METHYLAMPHETAMINE</td>
<td>150</td>
</tr>
<tr>
<td>METHYLENEDIOXYMETHYLAMPHETAMINE</td>
<td>150</td>
</tr>
<tr>
<td>PHENTERMINE</td>
<td>500</td>
</tr>
<tr>
<td>PSEUDOEPHEDRINE</td>
<td>500</td>
</tr>
<tr>
<td>BENZYLPIPERAZINE</td>
<td>500</td>
</tr>
<tr>
<td>11-NOR-DELTA-9-TETRAHYDROCANNABINOL-9-CARBOXYLIC ACID</td>
<td>15</td>
</tr>
<tr>
<td>BENZOYLECGONINE</td>
<td>150</td>
</tr>
<tr>
<td>ECGONINE METHYL ESTER</td>
<td>150</td>
</tr>
<tr>
<td>OXAZEPAM</td>
<td>200</td>
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<tr>
<td>TEMAZEPAM</td>
<td>200</td>
</tr>
<tr>
<td>DIAZEPAM</td>
<td>200</td>
</tr>
<tr>
<td>NORDIAZEPAM</td>
<td>200</td>
</tr>
<tr>
<td>ALPHA-HYDROXY-ALPRAZOLAM</td>
<td>100</td>
</tr>
<tr>
<td>7-AMINO-CLONAZEPAM</td>
<td>100</td>
</tr>
<tr>
<td>7-AMINO-FLUNITRAZEPAM</td>
<td>100</td>
</tr>
<tr>
<td>7-AMINO-NITRAZEPAM</td>
<td>100</td>
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TWO COMPARTMENT PHARMACOKINETIC MODEL

CENTRAL COMPARTMENT (CIRCULATORY SYSTEM)

ORAL DOSE → ABSORPTION

INTRAVENOUS DOSE → CENTRAL COMPARTMENT

EXCRETION

PERIPHERAL COMPARTMENT (TISSUE & ORGANS)

POTENTIAL RESERVOIR

METABOLISM